

WHAT IS CLAIMED IS:

1. A method of inducing a selective effect of a receptor comprising contacting the receptor with a compound that induces a nongenotropic effect without substantially inducing a genotropic effect, wherein the receptor is selected from the group consisting of a progesterone receptor, a glucocorticoid receptor, a mineralcorticoid receptor, a retinoic acid receptor, vitamin D receptor, PPAR receptor, pregnane X receptor, bile acid receptor, thyroid receptor, farnesoid X receptor, liver X receptor, ecdysone receptor, and COUP-TF receptor.
2. The method of claim 1, wherein the nongenotropic effect occurs due to the interaction of the compound with the ligand binding domain of the receptor.
3. The method of claim 1, wherein the nongenotropic effect occurs due to the activation by the compound of a region of the receptor which is the functional equivalent of the ligand binding domain of the estrogen receptor.
4. The method of claim 1, wherein the genotropic effect is mediated by the DNA-binding domain of the receptor.
5. The method of inducing a selective effect of a receptor comprising contacting the receptor with the compound that induces a genotropic effect without substantially inducing a nongenotropic effect.
6. The method of claim 5, wherein the receptor is selected from the group consisting of a progesterone receptor, a glucocorticoid receptor, a mineralcorticoid receptor, a retinoic acid receptor, vitamin D receptor, PPAR receptor, pregnane X receptor, bile acid receptor, thyroid receptor, farnesoid X receptor, liver X receptor, ecdysone receptor, and COUP-TF receptor.

7. The method of claim 5, wherein the genotropic effect is protein synthesis.

8. A method for screening a compound that will induce a selective nongenotropic effect of a steroid receptor comprising

5 assessing the ability of the compound to activate a pathway mediated by the ligand-binding domain of the steroid receptor without substantially activating the DNA-binding domain of the steroid receptor or to activate the DNA-binding domain of the steroid receptor without substantially activating functions mediated by the ligand-binding domain of the steroid receptor; and then

10 measuring the biological activity of the test compound to assess its ability to induce a target nongenotropic effect without substantially inducing a genotropic effect or its ability to induce a target genotropic effect without inducing a substantial nongenotropic effect.

15 9. The method of claim 8, wherein the steroid receptor is not the estrogen or progesterone receptor.

10. The method of claim 8, wherein the steroid receptor is selected from the group comprising a progesterone receptor, a glucocorticoid receptor, a mineralcorticoid  
20 receptor, a retinoic acid receptor, vitamin D receptor, PPAR receptor, pregnane X receptor, bile acid receptor, thyroid receptor, farnesoid X receptor, liver X receptor, ecdysone receptor, and COUP-TF receptor.

11. The method of inducing a selective effect of an estrogen receptor comprising  
25 contacting the estrogen receptor with a compound that induces a nongenotropic effect other than those mediated by the activation of extracellular regulated kinase without substantially inducing a genotropic effect.

12. The method of inducing a selective effect of an estrogen receptor comprising  
30 contacting the estrogen receptor with a compound that induces a nongenotropic effect

for other than the treatment of bone loss or to increase bone mass without substantially inducing a genotropic effect.

13. The method of inducing a selective effect of an androgen receptor comprising  
5 contacting the androgen receptor with said compound that induces a nongenotropic effect other than those mediated by the activation of extracellular regulated kinase without substantially inducing a genotropic effect.

14. The method of inducing a selective effect of an androgen receptor comprising  
10 contacting the androgen receptor with a compound that induces a nongenotropic effect for other than the treatment of bone loss or to increase bone mass or for the treatment of an estrogen-related cancer or endometreosis without substantially inducing a genotropic effect.

15. The method of inducing a nongenotropic effect of a steroid receptor, comprising administering a compound other than an estrogen or androgen containing a cyclopentanoperhydrophenanthrene nucleus which binds to the steroid receptor and induces a desired nongenotropic effect while not inducing a steroid-induced genotropic effect.

16. A method for screening a compound to select a compound that induces a selective steroidal response comprising:

contacting a steroid receptor with a test compound;

determining whether a test compound activates the nongenotropic activity of a  
25 receptor;

determining the level of transcriptional activity of the receptor-test compound complex; and

selecting the compound that activates the nongenotropic activity of the receptor and induces transcriptional activity of the receptor less than 10% of endogenous  
30 steroid receptor ligands.

17. The method of claim 16, wherein the nongentropic activity is preventing apoptosis.

18. The method of claim 16, wherein the nongentropic activity is a signal  
5 transduction pathway.

19. The method of claim 16, wherein the nongentropic activity is a second messenger system.

10 20. The method of claim 18, wherein the signal transduction pathway is a protein kinase signal transduction pathway.

21. The method of claim 20, wherein the protein kinase signal transduction pathway is a MAP kinase signal transduction pathway.

15 22. The method of claim 21, wherein the MAP kinase signal transduction pathway is the Src/Shc/extracellular regulated kinase signal transduction pathways.

23. A method of evaluating a compound comprising the steps of:

20 growing a tissue culture cell line until cell growth has reached appropriate confluence;

transfecting the tissue culture with an expression plasmid of a specific receptor and an expression plasmid for a target gene responsive to the selected receptor;

25 contacting the transfected cells with a test compound;

determining whether the compound induces a nongenotropic effect without substantially inducing a genotropic effect.

24. The method of claim 23, wherein the receptor is not an estrogen or  
30 progesterone receptor.

25. The method of claim 23, wherein the target gene is selected from the group consisting of chloramphenicol acetyl transferase (CAT),  $\beta$ -galactosidase, alkaline phosphatase, luciferase, peptide hormones, growth factors and chimeric proteins.

26. The method of claim 23, wherein the level of transcription of the target gene is determined using a method selected from the group consisting of calorimetric, fluorescent; immunochemical, chemical or radiochemical methods.

5 27. A method for screening compounds for the treatment of steroid receptor related diseases or disorders comprising:

contacting a cell expressing a selected natural or artificial steroid receptor with a test compound;

10 assessing whether the compound activates a nongentropic activity of the steroid receptor;

determining the level of transcription induced by the test compound;

and

15 selecting the compound or compounds that activate the nongentropic activity of the steroid receptor without substantially activating the genotropic activity of the steroid receptor.

28. A method for screening compounds for the treatment of steroid receptor related diseases or disorders comprising:

20 contacting a cell expressing a natural or artificial sex steroid receptor with a test compound alone or in combination with a pro-apoptotic agent;

assessing whether the compound activates a nongentropic activity of the steroid receptor;

determining the level of transcription induced by the test compound;

25 determining whether the test compound inhibited apoptosis in cells contacted with a test compound alone or in combination with a pro-apoptotic agent;

selecting the compound or compounds that activate the nongentropic activity of the steroid receptor without substantially activating the genotropic activity of the steroid receptor.

30 29. A method for screening for compounds that modulate the nongentropic activity of a steroid receptor without modulating the genotropic activity of the steroid receptor comprising the steps of:

contacting cells expressing a natural or artificial steroid receptor(s) with a test compound;

determining the amount of extracellular regulated kinase activation in the cells contacted with the test compound;

determining the amount of transcription in the cells contacted with the test compound;

5           selecting the cells contacted with the test compound that exhibit extracellular regulated kinase activation and minimal transcription levels as compared to transcriptions levels in cells contacted with an androgen or estrogen.

30.   A method for screening for compounds that modulate the nongentropic activity of a steroid receptor without modulating the genotropic activity of the steroid receptor comprising the steps of:

contacting cells with at least one test compound wherein the cells contain:

15           (a) non-endogenous DNA which expresses a steroid receptor protein, or functional engineered or modified forms thereof,

          (b) DNA which encodes an operative hormone response element linked to a first reporter gene; and

20           (c) DNA which encodes a second reporter gene operably linked to a signal transduction pathway responsive transcriptional control unit such that transcription of the second reporter gene is activated in response to activating a signal transduction pathway and wherein transcription of the second reporter gene is not activated by the steroid hormone;

assaying for evidence of transcription of the reporter genes in the cells;

and

25           selecting the compounds that induce transcription of the second reporter gene and do not induce transcription of the first reporter gene.

31.   A method for screening for compounds that modulate the nongentropic activity of a steroid receptor without modulating the genotropic activity of the steroid receptor comprising the steps of:

contacting cells with at least one test compound wherein the cells contain:

          (a) non-endogenous DNA which expresses a steroid receptor protein, or functional engineered or modified forms thereof,

(b) DNA which encodes a reporter gene operably linked to a signal transduction pathway responsive transcriptional control unit such that transcription of the reporter gene is activated in response to activating a signal transduction pathway and wherein transcription of the second reporter gene is not  
5 activated by the steroid hormone;

assaying for evidence of transcription of the reporter gene in the cells;

quantifying the transcription of steroid receptor responsive genes;

selecting the compounds that induce transcription of the reporter gene and do not induce transcription of steroid receptor responsive genes.

10 32. The method of claims 30 or 31, wherein the signal transduction pathway responsive transcriptional control unit is selected from the group consisting of serum response element, Activator protein 1, cAMP response element, E-box DNA binding element, E2F DNA binding element, glucocorticoid response element, heat shock  
15 response element, interferon  $\gamma$  activation sequence, interferon stimulated response element, nuclear factor of activated T cells, nuclear factor of  $\kappa$ B cells, p53 response element, Rb response element, and STAT3 response element.

33. A bioassay for identifying a test compound or chemical signal that activates  
20 nongentropic receptor activity without substantially activating genotropic receptor activity, comprising the steps of:

growing a tissue culture screening system in a chemically defined culture medium, optionally supplemented with nutrients, wherein the cell line of the tissue culture screening system contains a steroid receptor having at least one  
25 identified nongentropic activity;

adding a test compound or chemical signal to the medium;

measuring the amount of transcription;

measuring the amount of nongentropic activity;

30 selecting the compound that induces nongentropic activity but does not induce transcription.

34. The method of claim 33, wherein the cell line is OB-6.

35. A method of screening for ligands of steroid receptors that induce nongentropic activity without substantially inducing genotropic activity is provided comprising the steps of:

contacting a cell with a test compound wherein the cell has been transfected with :

i) a DNA sequence encoding a functional steroid receptor or genetic variant of a steroid receptor;

ii) a response element-reporter gene construct; and iii) serum response element-reporter gene construct;

determining the effect of the test compound on the transcription of the response element reporter gene construct;

determining the effect of the test compound on the transcription of the serum response element-reporter gene construct; and

selecting the compound that activates the transcription of the serum response element-reporter gene construct without substantially effecting the transcription of the response element reporter gene construct.

36. A method of screening for ligands of steroid receptors that induce nongentropic activity without substantially inducing genotropic activity is provided comprising the steps of:

contacting a first cell with a test compound wherein the first cell has been transfected with :

i) a DNA sequence encoding a functional steroid receptor or genetic variant of a steroid receptor;

ii) a response element-reporter gene construct;

determining the effect of the test compound on the transcription of the response element reporter gene construct;

contacting a second cell with the test compound wherein the second cell has been transfected with a signal transduction pathway responsive transcriptional control unit operably linked to a reporter gene;

determining the effect of the test compound on the transcription of the second cell; and

selecting the compound that activates the transcription of the second cell without substantially effecting the transcription of the first cell.



37. A kit for measuring steroid receptor dependent nongentropic activity comprising: a container having a stable transfected cell line wherein the cell line includes a steroid responsive reporter gene construct, a means for assessing the  
5 activation of nongentropic steroid activity, and a steroid receptor.